Performance Work Statement
National Academy of Sciences (NAS)
Contract #68HERC19D0011
PR-ORD-21-00431
PR-OCSPP-21-00045
Task Order: #68HERC21F0178

**I. TITLE:** Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for New Approach Methods (NAMs) for use in Human Health Risk Assessment

**II. Task Order Contracting Officer Representative(s):**

| **Task Order Contracting Officer Representative (TOCOR)** | **Alternate Task Order Contracting Officer Representative (Alt. TOCOR)** |
|---|---|
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**III. PERIOD OF PERFORMANCE:** Date of Task Order award through 24 months following award

**A. PURPOSE OF TASK ORDER**

The National Academy of Sciences (NAS) shall provide the Environmental Protection Agency (EPA) with a review of the variability and relevance of existing laboratory mammalian toxicity tests for human health risk assessment to inform the development of approaches for validation and establishing scientific confidence in using New Approach Methods (NAMs), and recommendations on expectations associated with NAMs when they cannot be compared with human studies, by hosting two (2) workshops and establishing an expert committee, described in the Scope of Work and Tasks 1-4 below.

**B. BACKGROUND**

In 2017, National Research Council (NRC) released a report entitled "Using 21st Century Science to Improve Risk-Related Evaluations." The risk-related applications report highlighted both the progress that had occurred in toxicology and exposure sciences since the release of previous

reports and identified several decision contexts that could benefit from application of the advances in the fields. It proposed a shift in thinking of the risk assessment community from whether a chemical causes a particular effect to whether a chemical increases the risk of a particular effect, while also recognizing that one does not need to know all the pathways or components involved in a particular disease to begin applying the new tools to regulatory decisions. The NRC Committee on Incorporating 21st Century Science into Risk-Based Evaluations also touched on the subject of validation and that many of the traditional processes for validation cannot match the pace of development of new assays, models, and test systems. The report recognized the challenges in validating a NAM where there is no "gold standard" or against toxicity tests that have not themselves been validated. The NRC Committee highlighted that there were two important issues on which there was still no consensus in the scientific community: 1) evaluation of the validity of assays that are not intended as one-to-one replacements for *in vivo* toxicity assays; and 2) assessment of the concordance of data from assays that use cells or proteins of human origin with toxicity data that are virtually all derived from animal models.

One of the important considerations in the evaluation of 'equivalent or better' approaches is that laboratory mammalian toxicity data provide a part of the foundation of the current risk assessment paradigm, and mammalian studies often provide the only available *in vivo* data for many environmental chemicals. There are a number of new evaluations of the qualitative and quantitative variability (Kleinstreuer *et al.*, 2016; Browne *et al.*, 2018; Pham *et al.*, 2020) and human relevance (e.g., Monticello *et al.*, 2017; Hoffmann *et al.*, 2018; Ackley *et al.*, 2019), of laboratory mammalian toxicity studies. These new studies highlight some of the limitations and challenges associated with using laboratory mammalian toxicity data as the standard benchmark for evaluating and implementing NAMs. Since the 2017 NRC report on 21st Century risk-related evaluations, the state of the science has continued to progress and the understanding and experience with NAMs has led to new considerations and more focused scientific questions. EPA is soliciting support from NAS to explore the strengths and limitations of using laboratory mammalian toxicology data as the benchmark for developing and evaluating NAMs, as well as possible novel approaches to validation and confidence building in using NAMs to replace mammalian toxicology data. This scientific exploration will become important in the policy decisions that EPA needs to address with "validation to ensure that NAMs are equivalent to or better than the animal tests replaced."

## C. SCOPE OF WORK

The NAS shall provide the EPA with a mechanism to recruit NAS identified subject-matter experts and when necessary, provide a forum for discussion(s) on science topics pertinent to using laboratory animal toxicology data as the benchmark for developing and evaluating NAMs. Forums may include either EPA or NAS-led meetings/workshops. EPA and NAS-led meetings and/or workshops shall address key science topics including, but not limited to new assessment methods (NAM); in vitro assay development and model systems toxicology; human health risk assessment; biostatistics; veterinary medicine and other scientific issues identified relevant for peer-review of draft assessment documents. The final product shall include data tables resulting from literature reviews as well as narrative comments pertaining to each section outlined below. The components of the review consist of the following:

1. **Variability and Human Relevance of Existing Laboratory Mammalian Toxicity Tests:**
   - Review the scientific literature pertaining to the qualitative and quantitative variability in laboratory mammalian toxicity tests.
   - Review the scientific literature on the overall concordance between laboratory mammalian models and humans in the adverse effects following exposure to commercial, environmental, and pharmaceutical chemicals, where available.
2. **Frameworks for Validation and Establishing Scientific Confidence:**
   - Review the scientific literature on validation of laboratory mammalian toxicity tests.
   - Review frameworks for establishing scientific confidence in NAMs.
   - Identify and describe the issues in the validation of NAMs as a replacement for existing laboratory mammalian toxicity tests.
   - Identify and describe the issues in the validation of NAMs that use cells or proteins of human origin in comparison to laboratory mammalian toxicity data.
   - Identify and describe the issues in the validation of NAMs that are not intended as one-to-one replacements for laboratory mammalian toxicity studies.
3. **Identification of Research Needs:**
   - Determine information gaps in the areas listed above to identify research priorities that could better inform these recommendations.

## D. CHARGE QUESTIONS TO THE EXPERT COMMITTEE

Specifically, the Committee shall answer and provide feedback on the following:

1. Does the Committee believe the literature review and data provided reflect a comprehensive, workable, objective, and transparent process?

2. Given the results of the literature review and workshops, what are the implications of the qualitative and quantitative variability of laboratory mammalian toxicity studies when using them to establish the performance of NAMs?

3. Given the results of the literature review and workshops, what is the concordance between laboratory mammalian models and humans in the adverse effects following chemical exposure and how might this frame expectations of NAMs when they cannot be compared directly with human studies?

4. The Committee shall impart expert advice on addressing the two related issues that were left unresolved in the 2017 NRC report:
   a. Evaluation of the validity of assays that are not intended as one-to-one replacements for in vivo toxicity assays; and
   b. Assessment of the concordance of data from assays that use cells or proteins of human origin with toxicity data that are virtually all derived from animal models.

5. Based on the conclusions from 1 – 4 above, how may the Committee foresee this information being incorporated into a new or the existing validation paradigm or scientific confidence framework so that EPA can ensure that NAMs are equivalent to or better than the animal tests replaced?

## E. DESCRIPTION OF TASKS

NAS' identified subject matter experts and committee members shall convene to complete the activities defined in this Performance Work Statement. The tasks are the following:

**Task 1 – Establish Public Workshops (Contract level PWS Task Area 2)**
The NAS shall establish two (2) public workshops. The first workshop shall focus on strengths and limitations with using laboratory animal toxicology data as the benchmark for developing and evaluating NAMs. The intent of the first workshop is to ensure a more consistent understanding of the issues and current scientific knowledge across the scientific and stakeholder communities. The second workshop shall provide input to the committee in support of the consensus report development. The NAS shall convene and facilitate the committee either via webinar or in-person if appropriate for deliberation following the public workshop and as needed to complete the final report. NAS shall provide recognized national and international experts an opportunity to discuss critical science topics relevant to scientific priorities.

***Subtask 1.1 – Initial meeting:*** Convene a meeting with the EPA and NAS to review the topics and issues to be discussed at the workshop(s). EPA will identify the topics and review issues via email anticipated to be discussed for each workshop approximately three to six (3-6) months before the workshop. If necessary, EPA will provide a one-pager with the necessary background information. This preliminary meeting shall occur within seven (7) days of EPA identifying the topics and anticipated issues.

***Subtask 1.2 – Establish a workshop agenda and a list of participants:*** NAS shall convene up to 15 experts to participate in the workshop. NAS shall identify and contact non-federal and federal subject matter experts who are (a) recognized experts in the field(s) and issues relevant to the workshop, (b) represent a range of recognized views on the issues identified by EPA, and (c) are available to present and discuss their research and individual views at the public workshop. Experts with an understanding of regulatory risk assessment (e.g., chemical hazards) are generally preferred. NAS shall provide the EPA TOCOR a proposed list of experts including a biographical sketch, proposed area of expertise for each expert, and if there are any issues regarding potential COI or impartiality. NAS shall convene a meeting with the EPA TOCOR and ORD management and technical staff to review the proposed list of experts. EPA may provide comments on the proposed list regarding qualifications and COI/impartiality. NAS shall determine who will participate in the workshop.

***Subtask 1.3. – Conduct the workshop(s):*** NAS shall convene and facilitate up to two (2) workshops to discuss topics and/or issues pertinent to assessment development. In coordination with the NAS, EPA will provide a general description of the desired goals and outcomes of each workshop. NAS shall provide EPA with a list of all registrants and participants after the workshop/meeting via email.

***Subtask 1.4. – Make arrangements for transportation, lodging and logistical support for each expert asked to participate in the workshop(s).***
NAS shall arrange provision for transportation, lodging, and any other logistical support for the experts' participation in the workshop(s)/meeting(s).

**Subtask 1.5 – Develop Workshop Outputs**
NAS shall develop one (1) rapporteur report for each workshop.

**Task 1 Deliverables**

a) For the workshops requested, the TOCOR shall be informed via email of the time, location, and agenda of the meeting at least 45 days prior to the meeting. All communications regarding public meetings should go through the TOCOR. The NAS shall provide EPA with a final list of all workshop attendees and public commenters within five (5) business days of the meeting (Subtask 1.2).
b) Arrangement and provision of transportation, lodging, and any other logistical support for the experts' participation in the workshops (Subtask 1.4).
c) If public websites or similar means are used to disseminate information to the public during the course of this task, the TOCOR shall be notified of the location of such information (e.g., websites), as well as relevant changes to them (Task 1).
d) Identified workshop report (Subtask 1.5).

**Task 2 – Convene Expert Committee (Contract level PWS Task Area 2)**

NAS shall identify and convene a proposed group of subject matter experts to serve on the committee, not to exceed sixteen (16) who are recognized experts in one or more of the fields relevant to the workshop including: in vitro assay development and model systems toxicology; human health risk assessment; biostatistics; and veterinary medicine. The EPA may offer suggestions of potential committee members to be considered by the NAS during its nominations process. EPA may also comment on the proposed committee membership during the 20-day comment period. The NAS will select the committee members.

***Subtask 2.1*: Perform literature review**

The NAS shall use a systematic approach to provide a review of published literature pertaining to the variability and human relevance of current laboratory mammalian toxicity tests and approaches to validation and establishing scientific confidence in using NAMs. The variability and relevance of the existing laboratory mammalian toxicity tests shall be considered by the NAS in terms of reliability, qualitative and quantitative reproducibility as well as biological relevance and overall concordance of the results in humans.

***Subtask 2.2*: Recruit Experts:** NAS shall identify a proposed group of subject matter experts to serve on the committee, not to exceed sixteen (16) who are (a) recognized experts in the field(s) relevant to the request, (b) represent a range of broadly recognized views on the issues identified by EPA, (c) are available to present and discuss their

individual views at the workshop, and (d) have been evaluated for conflict of interest or lack of impartiality.

***Subtask 2.3 – Post-Recruitment Notification:*** Provide the TOCOR a proposed list of SMEs including a biographical sketch and proposed area of expertise for each SME. NAS will evaluate any issues regarding potential conflict of interest (COI) or impartiality.

EPA may provide comments on the provisional committee appointments during the 20-day public comment period. NAS shall determine who will participate in each workshop. NAS shall then deliver a final list of participants.

***Subtask 2.4 – Expert Logistic Support:*** NAS shall coordinate workshop logistics information (e.g., webinar and teleconference information) between EPA and the SMEs. Generally, these workshops are expected to be conducted via webinar but if necessary, NAS shall make arrangements for transportation, lodging and logistical support for each SMEs asked to participate in the workshop to be held in Washington, D.C.-or another location as specified by EPA-for up to two (2) workshops.

***Subtask 2.5 – Comment Compilation:*** NAS shall compile non-consensus input from each SME on topics discussed at the workshop for delivery to the TOCOR.

**Task 2 Deliverables**

a) The primary products for each workshop are expected to be: (a) proposed and final lists of experts including biographical sketches, which will participate in each of the two (2) workshops specified by EPA, and (b) develop a document of compiled comments from each expert to provide to EPA that may be published externally (Task 2).
b) Participation of the experts in NAS workshops. Arrangement and provision of transportation, lodging, and any other logistical support for the experts' participation in the workshops (Task 2).

**Task 3 – Write Report**

The NAS shall write a report presenting the NAS committee's findings regarding the charge questions and the results of both workshops and the process followed by the committee to develop those findings and recommendations shall be delivered prior to expiration of this task order.

***Subtask 3.1:*** **Conduct an independent peer review**

NAS shall conduct an independent peer review for a final report. In coordination with NAS, EPA will transmit the external peer review assessment materials, prior to the peer review. EPA also requests that NAS organize an external peer review meeting(s) for the peer review committee to discuss the draft assessment with EPA and to include an opportunity for public comment.

***Subtask 3.2:*** **Deliver Final Report**

NAS shall deliver a final report presenting the NAS Committees findings regarding the charge questions and the results of both workshops.

**Task 3 Deliverables**

a) If public websites or similar means are used to disseminate information to the public during the course of this task, the TOCOR shall be notified of the location of such information (e.g., websites), as well as relevant changes to them (Task 3).
b) Peer reviewed final report detailing the NAS committee's findings regarding the charge questions to the committee. (Subtask 3.2)

**Task 4 – Monthly Progress Reports to TOCOR**

The contractor shall write and submit monthly progress reports to the TOCOR. Progress reports shall describe completed work during the invoice period and should link to charges described in invoice documentation.

***Subtask 4.1:*** **Deliver Monthly Progress Reports to TOCOR**

Monthly progress reports shall include a written monthly technical progress report that includes the following: (a) an overview of work accomplished since project inception; (b) a description of work accomplished during the reporting period; (c) a summary of QA/QC activities since project inception including a summary of corrective action taken; (d) a brief summary of anticipated work during the following period; (e) a summary and details of the costs incurred for each task during the quarter and cumulatively; and (f) total remaining budget. Routine progress reports shall be delivered electronically; paper copies are not required.

**Task 4 Deliverables**

a) EPA requests that written progress reports be provided to TOCOR monthly including an update of the project milestones. (Subtask 4.1)

## F. COVID Considerations

If appropriate, the NAS may conduct the workshops as face-to-face meetings. Options for face-to-face and virtual meetings may be included in the proposal.

**G. ACCEPTANCE CRITERIA**

The Contractor shall prepare high quality products and that are reproducible and transparent. Figures submitted shall be of high quality similar to presentations developed for national scientific forums to be formatted as jpeg or TIFF files. Deliverables shall be edited for grammar, spelling, and logic flow as well as, technical accuracy, completeness, timeliness, grammatically correct, free of typographical errors, and conformance with the specific task, charge and expertise and deliverables of this Performance Work Statement. The technical information shall be reasonable complete and presented in a logical, readable manner. Text deliverables shall be provided in Microsoft Word 2016 and *Adobe Acrobat*, or compatible formats. Deliverables will be accepted upon review and approval by the TOCOR.

**H. EPA Technical Experts:** Russell Thomas and Nisha Sipes